REMARKS/ARGUMENTS

Claim Status/Support For Amendments

In response to the Office Action of April 23, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

No new matter has been added by the amendments to the specification.

The title of the application has been amended to more clearly indicate the invention to which the pending claims are drawn.

Several protocols in the experimental section of the detailed description have been amended to properly identify the trademark SEPHAROSE.

A section of the detailed description was amended to correct typographical errors.

The abstract has been amended to remove the legal phraseology ("said").

Claim 1 has been amended. Claims 2-38 have been canceled. Claims 39-46 have been added. Claims 1 and 39-46 are pending in the instant application. As stated herein under the heading **Restriction/Election and Request for Rejoining of Claims** (see p.11), the election of the Group I invention is affirmed, claim 1 now constituting said Group I invention as claims 2 and 10-28 originally included in Group I have been canceled. As later explained, if claim 1 is deemed to be allowable, rejoinder of the

remaining claims (39-46) in accordance with *Ochiai* is respectfully requested.

No new matter has been added by the addition of new claims 39-46. The subject matter of new claims 39-46 corresponds with the subject matter of cancelled claims 2-38. The above additions to the claims also find basis in the original disclosure at page 25, line 16 to page 26, line 22. The method of new claim 39 is described in detail at pages 37-47. Page 47, line 23 to page 48, line 4, refers to use of various types of samples and page 38, line 22 to page 39, line 12 refers to different mass spectrometric techniques. Page 46, line 23 refers to practicing the claimed methods with a human patient. Pages 47-48 describe kits contemplated for use with the claimed methods. Lines 18-23 on page 47 refer particularly to the immobilizing on solid supports and labeling of components of the contemplated kits. It is clear from these specific recitations and from the description of methods utilized that the methods and types of kits recited in the newly added claims (39-46) were fully contemplated by the inventors at the time of filing and were enabled by virtue of the disclosure as originally filed.

Restriction/Election and Request for Rejoining of Claims

Applicants herein affirm the election of Group I (claims 1, 2 and 10-28) without traverse for prosecution on the merits. The election was made during a telephone conference with the Examiner

on January 15, 2003.

The instant application is related in claim format to several pending applications of which serial number 09/846,352 is exemplary. The biopolymer marker of serial number 09/846,352 was found to be novel and subsequently claims reading on methods and kits limited to its use were rejoined with the claims reading on the biopolymer marker under *Ochiai*. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner enter new claims 39-46 in the instant application as being drawn to a non-elected invention and consider joining them (new claims 39-46) with claim 1 of the elected invention (Group 1) upon the Examiner's determination that the claim of the elected invention is allowable, since if the peptides consisting of amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3 are found to be novel, methods and kits limited to their use should also be found novel.

Sequence compliance

Applicants have reviewed the entire specification including the figures and the claims for sequence disclosures. The only sequences found to be disclosed are the amino acid sequences identified as SEQ ID NOS:1-3. On page 46 of the original disclosure, the first and last amino acid residues of each of SEQ

ID NOS:1-3 are shown in parentheses. When carrying out mass spectrometric procedures, it is possible to fragment a whole molecule, depending upon the enzyme used for digestion. A sequence is often predicted from these fragments but often the sequence is not identified completely. It is conventional in the art to show the missing portions of the predicted sequence in parentheses. The first and last amino acid residues of SEQ ID NOS:1-3 are predicted residues as disclosed by the parentheses on page 46 of the original disclosure. Thus, no new matter is added. The first and last amino acid residues of SEQ ID NOS:1-3 are disclosed in the Sequence Listing, however the biopolymer marker peptides identified as markers in patient sera consist of amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3. The amendments to the claims and specification limiting the marker sequences to specific amino acid residues are made for the purpose of clarification of the use of parentheses only. The claims as herein amended limit the biopolymer marker peptide sequences to amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3.

Rejections under 35 USC 112 (second paragraph)

Claims 1, 2 and 10-28, as originally presented, stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for

allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claims 1, 10, 18 and 28 are vague and confusing in reciting the phrase " at least one analyte thereof" because it is unclear how a material can be an analyte of a biopolymer marker. Claim 1 has been amended and does not recite the phrase "at least one analyte thereof". Claims 10, 18 and 28 have been canceled and the phrase "analyte thereof" is not recited in any of the remaining pending claims.

The Examiner alleges that claim 1 is vague and indefinite in reciting the phrase "indicating at least one particular disease state" because it is unclear what specific disease(s) applicant refers to. Claim 1 has been amended to delete the phrase "indicating at least one particular disease state" and to specifically recite the disease state of insulin resistance.

The Examiner alleges that claim 2 should recite the phrase "of insulin" in place of "if insulin". Claim 2 has been canceled, thus rendering this rejection moot.

The Examiner alleges that claims 12 and 14 are vague and indefinite in relation to claim 10 in reciting "at least one labeled biochemical material" because it is unclear as to whether the biochemical material in claims 12 and 14 is the same as the biochemical material recited in claim 10, but including a label. Claims 12 and 14 have been canceled and the phrase "at least one

labeled biochemical material" is not recited in any of the remaining pending claims.

The Examiner alleges that the term "therefore" in claims 17 and 25 should be --thereof--. Claims 17 and 25 have been canceled and neither "therefore" nor --thereof-- is recited in any of the remaining pending claims.

The Examiner alleges that the term "the sample" in claims 23 and 24 lacks antecedent basis. Claims 23 and 24 have been canceled, thus rendering this rejection moot.

Accordingly, applicants have now clarified the metes and bounds of the claims and respectfully request that all of the above-discussed rejections under 35 U.S.C. 112, second paragraph be withdrawn.

Rejection under 35 USC 101

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 101 because the claimed invention is allegedly not supported by either a credible asserted utility or a well-established utility.

The Examiner alleges that the asserted utility of the biomarkers of claims 1 and 2 is for indicating at least one particular disease state, i.e. use in a diagnostic method. However, the Examiner alleges that Applicant fails to present concrete and convincing evidence recognized in the art in support of the

asserted diagnostic method by using the recited amino acid biomarkers. The Examiner indicates that the prior art has identified SEQ ID NOS:1 and 2 as indicators of fatty acid metabolism and psychological disorders, respectively, other than the asserted indicative of insulin resistance.

Applicants respectfully disagree with the Examiner's assertions. Claim 2 has been canceled and the subject matter incorporated into amended claim 1. It is clear that claim 1 is limited to specific biopolymer marker peptides (amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3) specifically diagnostic for insulin resistance. The phrase "diagnostic for insulin resistance" constitutes a specific and substantial utility for the claimed peptides. The Examiner is reminded that applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement (see MPEP 2107, II, B (1) (ii)).

Applicants provide a general disclosure of the protocols and methods used to identify the claimed biopolymer marker peptides at pages 37-40 of the instant specification. Pages 40-45 of the instant specification provide specific steps and protocols one would carry out in order to identify the claimed biopolymer marker peptides. Furthermore, electrophoretic, chromatographic and mass spectrometric techniques are well-known to one of skill in the art,

thus even if specific protocols were not included within the disclosure, one of skill in the art would know how to carry out the protocols in the instant disclosure. Applicant is not required to describe what is well known in the art. A patent need not teach, and preferably omits, what is well known in the art (see MPEP 2164.01).

According to the method of the instant invention; biological samples(types of samples are listed at page 47, line 23 to page 48, line 4 of the instant specification) are obtained from both patients having a disease condition and healthy (normal) patients. The samples are resolved by polyacrylamide gel electrophoresis and the resulting protein bands appearing from the diseased samples are compared with protein bands appearing from the normal samples. Bands which differ between the samples are cut from the gel(see abstract of the disclosure for a general statement of this principle). The proteins of the excised bands are then subjected to enzymatic digestion, chromatography and identification by mass spectrometric techniques. For example, band 6 shown in lane 4 (as read from the left) of the gel shown in Figure 3 was present in a sample obtained from a patient suffering from insulin resistance (as noted on the label under the lane). Band 6 was then excised and subjected to the above-noted protocol of the instant invention. The peptide consisting of amino acid residues 2-13 of SEQ ID NO:3 was identified as a fragment of adrenergic alpha 2A receptor excised

from band 6 of Figure 3. Since this fragment (amino acid residues 2-13 of SEQ ID NO:3) was present in a sample obtained from a patient suffering from insulin resistance and not present in samples obtained from the healthy patients (lanes 6-9 as read from the left); amino acid residues 2-13 of SEQ ID NO:3 is considered to be indicative of insulin resistance.

Thus, one of ordinary skill in the art would recognize from the protocols and figures disclosed in the instant specification that the claimed biopolymer marker peptides are diagnostic of insulin resistance. Applicants respectfully submit that they have presented concrete and convincing evidence, which is fully disclosed in the instant specification, to support the diagnostic utility of the claimed biopolymer marker peptides.

The Examiner states that the prior art has identified SEQ ID NOS:1 and 2 as indicators of fatty acid metabolism and psychological disorders which are distinct from the asserted indication of insulin resistance. The pending claims are drawn to specific biopolymer marker peptides specifically diagnostic for insulin resistance. Applicants neither claim nor exclude other utilities for the claimed biopolymer marker peptides. Thus, the fact that the prior art discloses SEQ ID NOS:1 and 2 as indicators of fatty acid metabolism and psychological disorders is irrelevant to the instant invention as recited in the remaining pending claims.

product claim
No patentable weight

Accordingly, it is respectfully submitted that the Applicants have now shown that the claimed invention is supported by a credible asserted utility. Thus, Applicants respectfully request that the above-rejection under 35 U.S.C. 101 be withdrawn.

Rejection under 35 USC 112 (first paragraph)

Claims 10-28, as originally presented, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 10-28 have been canceled, however the subject matter of canceled claims 10-28 is incorporated into the claims (39-46) added herein by amendment, thus this rejection is addressed.

The Examiner asserts that the prior art fails to disclose a method for predicting insulin resistance disease state. Applicants respectfully disagree with the Examiner's assertion. The remaining pending claims are now limited to methods and kits using specific biopolymer markers (amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3) specifically diagnostic for insulin resistance. Applicants are not claiming the ability to predict insulin resistance or any other disease state. Applicants are not required

to enable material that is not claimed (see MPEP 2164.08). The instant inventors do not attempt to develop a reference "normal", but rather strive to specify particular markers which are evidentiary of at least one specific disease state, whereby the presence of said marker serves as a positive indicator of disease (see page 5, lines 12-20 of the instant specification). Applicants claim that the presence of a peptide selected from the group consisting of amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3 is a positive indicator of insulin resistance.

The Examiner further asserts that there is a lack of sufficient support that the instant recited SEQ ID NOS:1-3 can be unequivocally served as the biomarkers for insulin resistance. Applicants respectfully disagree with the Examiner's assertions. Applicants are not asserting that the claimed peptides are the only existing biomarkers of insulin resistance. Applicants are not required to enable material that is not claimed (see MPEP 2164.08).

Furthermore, applicants provide a general disclosure of the protocols and methods used to identify the claimed biopolymer marker peptides at pages 37-40 of the instant specification. Pages 40-45 of the instant specification provide specific steps and protocols one would carry out in order to identify the claimed biopolymer marker peptides. Electrophoretic, chromatographic and mass spectrometric techniques are well-known to one of skill in the

art, thus even if specific protocols were not included within the disclosure, one of skill in the art would know how to carry out the protocols in the instant disclosure. Applicant is not required to describe what is well known in the art. A patent need not teach, and preferably omits, what is well known in the art (see MPEP 2164.01).

Applicants clearly teach in the instant specification how the claimed peptides were determined to be diagnostic for insulin resistance and further set forth a protocol which can be followed to determine markers of any disease condition. For example, according to the method of the instant invention; biological samples(types of samples are listed at page 47, line 23 to page 48, line 4 of the instant specification) are obtained from both patients having a disease condition and healthy (normal) patients. The samples are resolved by polyacrylamide gel electrophoresis and the resulting protein bands appearing from the diseased samples are compared with protein bands appearing from the normal samples. Bands which differ between the samples are cut from the gel. The proteins of the excised bands are then subjected to enzymatic digestion, chromatography and identification by mass spectrometric techniques. For example, band 6 shown in lane 4 (as read from the left) of the gel shown in Figure 3 was present in a sample obtained from a patient suffering from insulin resistance (as noted on the label under the lane). Band 6 was then excised and subjected to the

above-noted protocol of the instant invention. The peptide consisting of amino acid residues 2-13 of SEQ ID NO:3 was identified as a fragment of adrenergic alpha 2A receptor excised from band 6 of Figure 3. Since this fragment (amino acid residues 2-13 of SEQ ID NO:3) was present in a sample obtained from a patient suffering from insulin resistance and not present in samples obtained from the healthy patients (lanes 6-9 as read from the left); amino acid residues 2-13 of SEQ ID NO:3 is considered to be indicative of insulin resistance.

Thus, Applicants respectfully submit that the instant specification provides sufficient guidance on how to identify and use the claimed peptides as biomarkers of insulin resistance.

The Examiner further asserts that there are "fatal defects" that fail to enable the instant invention.

The first "fatal defect" cited by the Examiner is that it is not clear how many patient samples were used in this experiment. Applicants respectfully disagree, since lanes 2-9 of the gels are labeled with patient conditions in figures 1 and 3. Thus, it is clear that 8 patient samples were used in the experiment represented by figure 1; 5 disease samples (lanes 2-6) and 3 normal samples (lanes 7-9). It is also clear that 8 patient samples were used in the experiment represented by figure 3; 4 disease samples (lanes 2-5) and 4 normal samples (lanes 6-9). Furthermore, Applicants are not claiming any correlation of the markers with

development of insulin resistance, they are claiming that the presence of the markers in a patient sample is a positive indicator of insulin resistance.

The second "fatal defect" cited by the Examiner is that it is not clear how figure 1 was conducted or what source of samples were used. Figure 1 is obviously a photograph of an electrophoresis gel. The general procedure for running the gels is shown at page 38 of the instant specification. Electrophoresis is a standard technique used for separation of biological components and thus one of ordinary skill in the art would be familiar with this technique. Additionally, it is believed to be clear that the source of the samples is blood (sera), for example, the gel shown in figure 1 results from the HiQ 1 (elution) column, the protocol for which is shown at page 43, beginning at line 5, wherein it shows clearly in step 1 that the sample is sera.

The third "fatal defect" cited by the Examiner is that no evidence supports the notion that appearing a different protein certainly attributes to the occurrence of a particular disease. Applicants are not claiming that the peptide markers attribute to the occurrence of a particular disease; Applicants are claiming that the presence of the peptide markers is indicative of insulin resistance. Applicants are not required to enable material that is not claimed (see MPEP 2164.08).

The Examiner further states that there is a lot of uncertain

"missing boxes", *e.g.* different physiological or pathological developments, from protein synthesis down to the phenotype of the specified disease. Applicants claim that the presence of a peptide selected from the group consisting of amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3 is a positive indicator of insulin resistance. Applicants are not required to explain the disease process in insulin resistance; Applicants are only required to show that the claimed peptides are indicative of insulin resistance (see MPEP 2165.03). The figures of the instant disclosure show that the claimed peptides are indicative of insulin resistance.

The fourth "fatal defect" cited by the Examiner is that it is not clear what bands appeared on the gel of figure 1 correspond to SEQ ID NOS:1-3. Also, it is not clear what bands are down or upregulated as corresponding to insulin resistance. None of the bands on either gel (figure 1 or figure 3) correspond directly to the claimed peptides. The bands represent whole proteins or groups of proteins as they are separated from the patient sample. The claimed peptides are fragments of whole proteins excised from the gel. The whole proteins excised from the gel are subjected to enzymatic digestion and subsequent identification (of the digested fragments) by use of mass spectrometric techniques. As noted by the legends in the figures; band 3 of figure 1 contains the peptide fragment of SEQ ID NO:2 and band 6 of figure 3 contains the peptide

fragment of SEQ ID NO:3.

There is no conventional control applied in the methods of the instant invention. Both samples from diseased patients and samples from healthy patients are separated by gel electrophoresis. The bands which differ between diseased and healthy are excised. A determination of upregulation or down regulation of the proteins present in the bands is assessed by sample wherein they appear, for example, the claimed peptide fragments were excised from bands which appeared in the diseased samples, thus this can be considered to be upregulation of the protein in the disease state.

A Declaration Under 37 CFR 1.132 is submitted herewith in order to clarify the use of controls in the experiments disclosed in the specification.

The fifth "fatal defect" cited by the Examiner is that the instant specification lacks specificity to differentiate the insulin-related resistance disease. The Examiner states that to be a specific biomarker for a particular disease, the marker must be specific to distinguish one disease from another to avoid false positive results. Applicants are not claiming the ability to distinguish between disease states or to distinguish between the insulin-related resistance diseases. Applicants are not required to enable material that is not claimed (see MPEP 2164.08). The claimed biopolymer marker peptides are considered to be positive indicators of any insulin-resistance disease.

Accordingly, as demonstrated in the above-discussion, applicants assert that one of ordinary skill in the art when reviewing the instant specification would recognize how to use the claimed sequences(amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3) as markers for insulin resistance. Thus, Applicants respectfully request that this rejection now be withdrawn.

Rejections under 35 USC 102(b)

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Borden *et al.* (WO 96/04790).

The Examiner asserts that Borden *et al.* teach using mammalian betaine gamma-aminobutyric acid transporter comprising the recited SEQ ID NO:2 (see SEQ ID NO:1. residues 583-595). The Examiner alleges that Borden *et al.* also teach using the markers for screening and diagnosis of GABA-associated abnormalities.

Applicants respectfully disagree with the Examiner's assertions. Claim 2 has been canceled and the subject matter incorporated into amended claim 1. Claim 1 has been amended to recite specific biopolymer marker peptides (amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3) specifically diagnostic for insulin resistance. Thus, claim 1 now recites specific peptides

with a specific function or use.

SEQ ID NO:1 as disclosed by Borden *et al.* contains 2217 residues which encode the entire human betaine/GABA transporter protein while the instant invention discloses a fragment comprising 14 residues of human betaine/GABA transporter protein. Claim 1 has been amended to recite the phrase "consisting of". Since "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claim now encompasses only these specific peptides(amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3)having this specific function (diagnostic for insulin resistance), thus excluding the sequences as described by Borden *et al.*

Furthermore, no where does Borden *et al.* teach the claimed fragment (amino acid residues 2-12 of SEQ ID NO:2). Nor does Borden *et al.* teach that their SEQ ID NO: 1 or any fragment thereof is diagnostic for insulin resistance.

Accordingly, Applicants respectfully submit that the claim, as instantly presented, now distinguishes over the compositions taught by Borden *et al.* and respectfully request that this rejection now be withdrawn.

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Ferdinandusse *et al.* (Biochemical and Biophysical Research Communications 263:213-218 1999).

The Examiner alleges that Ferdinandusse *et al.* teach cloning human carnitine octanoyl transferase comprising the recited SEQ ID NO:1 (see residues 187-198).

Applicants respectfully disagree with the Examiner's assertions. Claim 2 has been canceled and the subject matter incorporated into amended claim 1. Claim 1 has been amended to recite specific biopolymer marker peptides (amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3) specifically diagnostic for insulin resistance. Thus, claim 1 now recites specific peptides with a specific function or use.

Ferdinandusse *et al.* teach a 613 residue sequence in Figure 1 which encodes the entire human carnitine octanoyl transferase while the instant invention disclose a 12 residue fragment of human carnitine octanoyl transferase. Claim 1 has been amended to recite the phrase "consisting of". Since "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claim now encompasses only these specific peptides (amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino

acid residues 2-13 of SEQ ID NO:3)having this specific function (diagnostic for insulin reistance), thus excluding the sequences as described by Ferdinandusse *et al.*

Furthermore, no where does Ferdinandusse *et al.* teach the claimed fragment (amino acid residues 2-11 of SEQ ID NO:1). Nor does Ferdinandusse *et al.* teach that their sequence or any fragment thereof is diagnostic for insulin resistance.

Accordingly, Applicants respectfully submit that the claim, as instantly presented, now distinguishes over the compositions taught by Ferdinandusse *et al.* and respectfully request that this rejection now be withdrawn.

Rejection under 35 USC 103(a)

Claims 1, 2 and 10-28, as originally presented, stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Borden *et al.* (WO 96/04790) in view of Hutchens *et al.* (US 6,225,047 B1).

The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time that the instant invention was made to combine the teaching of Borden *et al.* of SEQ ID NO:2 which comprises a biopolymer used as a diagnostic marker of a disease state with the method of Hutchens *et al.* which uses SELDI-MS for differential detection of biopolymers by antibody binding to the specific analyte because the teachings of Hutchens *et al.* specifically teach to resolve different biomarkers for clinical

diagnostic purposes.

Applicants respectfully disagree with the Examiner's assertions. Claims 10-28 have been canceled. Claim 2 has been canceled and the subject matter incorporated into amended claim 1. SEQ ID NO:1 as disclosed by Borden *et al.* contains 2217 residues which encode the entire human betaine/GABA transporter protein while the instant invention discloses a fragment comprising 14 residues of human betaine/GABA transporter protein. Claim 1, as amended herein, recites the phrase "consisting of" and thus now encompasses only specific peptides(amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3) with a specific function (diagnostic for insulin resistance). No where does Borden *et al.* teach the specific peptides of the instant invention or any other specific fragments of human betaine/GABA transporter protein. Additionally, Borden *et al.* do not teach any human betaine/GABA transporter protein sequence or any portion thereof which is diagnostic for insulin resistance. Thus, it is established that Borden *et al.* do not teach any biopolymer markers diagnostic for insulin resistance.

Hutchens *et al.* teach a method for identifying analytes that are differentially present between two samples through the use of the techniques of retentate chromatography and desorption spectrometry. Although the instant invention also teaches a method for identifying analytes that are differentially present between

two samples through the use of the techniques of chromatography and spectrometry, the chromatographic methods of the instant invention are distinct from retentate chromatography. Page 45, line 6 of the instant specification refers to the use of micro-chromatographic columns which evidences the use of a form of chromatography known as partition chromatography. Partition chromatography and retentate chromatography are not identical methods. Retentate chromatography is limited by the fact that if unfractionated body fluids (blood, blood products, saliva, urine, cerebrospinal fluid and lymph) along with tissue samples, are applied to the adsorbent surfaces, the biopolymers present in the greatest abundance will compete for all the available binding sites and thereby prevent or preclude less abundant biopolymers from interacting with them, thereby reducing or eliminating the diversity of biopolymers which are readily ascertainable (see the instant specification at pages 24 and 25). The instant invention is characterized by the use of a combination of preparatory steps (chromatography and 1-D tricine polyacrylamide gel electrophoresis) that maximizes the diversity of biopolymers discernable from a sample thus overcoming the limitation of the retentate chromatography method as taught by Hutchens *et al.* Furthermore, Hutchens *et al.* do not suggest alternative means for the identification of differentially present analytes nor do they suggest preparatory steps to overcome the limitations of retentate chromatography. Thus, even if Borden *et al.* did disclose biopolymer

markers diagnostic for insulin resistance and one of ordinary skill in the art identified such markers through use of the methods as taught by Hutchens *et al.*, one of ordinary skill in the art would not have arrived at the instant invention.

There are no teachings or suggestions in either reference (Borden *et al.* and Hutchens *et al.*) which would motivate one of ordinary skill in the art to use preparatory steps in combination with methods of chromatography and spectrometry to identify any biopolymer markers diagnostic for insulin resistance.

Thus, it is respectfully submitted that the combination of Borden *et al.* in view of Hutchens *et al.* fails to reasonably teach or suggest to one of ordinary skill in the art the elements of the invention as specifically set forth in the instantly amended claims.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

Ferris H. Lander

Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)

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